REMARKS

Claims 1-25 are pending in the application. Claims 11-25 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1 and 2 have been amended to better clarify what Applicants believe to be the invention. Support for the amendment to claims 1 and 2 can be found throughout the specification, but particularly in Table 3, pages 19-21 and Table 4, page 37, and further on page 43, paragraph [0136], on page 44, paragraphs [0146], [0145] and [0150]. No new matter has been entered by way of this amendment. Accordingly, claims 1-10 are currently under consideration.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 1, and 3-10 under 35 U.S.C. 112, first paragraph for lack of enablement. More particularly, the Examiner alleges that while the specification is enabled for treating hepatitis, it does not reasonably provide enablement for treating immunological disorders. The Examiner asserts that the specification does not enable any person skilled in the art to use the invention commensurate in scope with the claims.

The Examiner alleges that inventions targeted for treating immunological disorders bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. Moreover, the standard of enablement is high for such inventions because effective treatments for these disease conditions are relatively rare, and may be unbelievable in the absence of strong supporting evidence. The Examiner alleges that while Applicant claims compositions for treating immunological disorders, the specification provides no working examples and no guidance that would permit the skilled artisan to practice the invention commensurate with the scope of the instant claims. Moreover, the Examiner alleges that the data found in the specification is inconclusive to support the breadth of the claimed invention. The Examiner further alleges that without specific examples or guidance in the specification for treating immunological disorders, or without teachings in the art that are supportive of the efficacy of the compositions, the claims would require undue experimentation without a predictable degree of success on the part of the skilled artisan.

Applicants respectfully traverse the Examiner's rejection and have amended the claims to recite that the compositions are useful for increasing the number of immune cells and platelets in patients having advanced stage hepatitis characterized by fibrosis and cirrhosis in stages 4-6 of the disease process. Support and enablement for this aspect of the invention can be found page 43, paragraph [0136], on page 44, paragraphs [0146], [0145] and [0150]. More particularly, Applicants have demonstrated that the compositions of the invention increase the number of T helper cells (CD4+) and T suppressor cells (CD8+), as well as the number of B lymphoid cells, natural killer cells and platelets in a mammal. Applicants assert that while certain of the immunological parameters of the studies presented herein were performed in rats, similar analyses were carried out in the patients having advanced stage hepatitis, more particularly patients showing evidence of liver fibrosis and cirrhosis. In addition, Applicants further assert that it would not take undue experimentation to perform the same studies in humans other than those suffering from late stage hepatitis. In fact, the practice of assessing various immunomodulators in humans, particularly in patients suffering from HIV/AIDS, by looking at the number of T cells bearing the CD4+ and CD8+ markers is a common practice. The same holds true for cells of B cell lineage and natural killer cells. There are standard markers available for assessing the number or percentage of immune cells in humans bearing markers for cells of both the T and B cell lineage, as well as natural killer cells. Applicants assert that it would not take undue experimentation for the skilled artisan to determine the number of T cells, B cells or NK cells in a human patient, other than those currently tested, after administration of Ambovex. The use of specific T, B and NK cell markers is common practice for one practicing the art of immunology. Furthermore, the numbers of cells expressing these markers can be determined quite easily, using methods known to those skilled in the art, in particular, by manual counting or by use of a fluorescent activated cell sorter. However, in the interest of putting the application in condition for allowance, Applicant has amended the claim to recite:

"A pharmaceutical composition for treating patients having advanced stage hepatitis characterized by fibrosis and cirrhosis and for increasing the number of immune cells and platelets in patients having advanced stage hepatitis characterized by fibrosis and cirrhosis, ..."

Further support for enablement of this can be found in the attached declaration under 37 CFR 1.132, signed by Dr. Ismail Elchagea, which includes results of clinical trials in patients having advanced stage hepatitis, who were treated with the plant extract of the present invention (Ambovex). As shown in this declaration, significant effects of the plant composition on hepatitis viral titers were observed (Figure 1), as were effects on liver function tests (Figure 2), fibrotic progression (Figures 3 and 4), histopathology (Figures 5 and 6), and on immunopathology, specifically significant effects on immune cells including T cells, Macrophages, and natural killer cells (Figures 7-10), all attached herewith as Exhibit A.

Based on the foregoing, withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. §102

A. Claims 1, 2, 4-6, and 6-10 have been rejected under 35 U.S.C. 102(b) as being unpatentable over Medenica (U.S. 5,653,981). The Examiner alleges that Medenica teaches using an extract of *Nigella sativa* for increasing immune system function. The Examiner further alleges that Medenica also teaches how to administer the extract of *Nigella sativa* such as intramuscular, subcutaneous, intravenous, tablet, capsule, or suppositories or the like.

Applicants' Invention as Currently Claimed

The present invention, as currently claimed, is directed to a pharmaceutical composition for treating patients having advanced stage hepatitis characterized by fibrosis and cirrhosis and for increasing the number of immune cells and platelets in patients having advanced stage hepatitis characterized by fibrosis and cirrhosis, comprising a therapeutically effective amount of at least one of the botanical plants selected from the group consisting of Actaea rubra, Anemone hepatica, Anemone nemorosa, Nigella sativa, and Ranunculus arvensis, or extracts thereof, and a pharmaceutically acceptable carrier, wherein the patients having advanced stage hepatitis are in stages 4 through 6 of the disease process. The composition may be delivered as a tablet or capsule, or in the form of a liquid or suspension. It may be delivered

intramuscularly, subcutaneously, intravenously, intranasally, topically, transdermally, or in the form of a suppository.

More particularly, the claims have been amended to recite that the compositions are used to treat **advanced staged hepatitis patients**, whereby patients at this late stage of the disease process have **fibrosis and cirrhosis** of the liver or for increasing immune cells and platelets in this patient population.

Medenica

The Examiner alleges that Medenica teaches using an extract of *Nigella sativa* for increasing immune system function. The Examiner further alleges that Medenica teaches that the extract of *Nigella sativa* may be administered intramuscularly, subcutaneously, intravenously, by tablet, by capsule, or suppositories.

Claim Amendments and Arguments in Support of Patentability over Medenica

Applicants respectfully traverse the Examiner's rejection and assert that in order for a rejection under 35 U.S.C. 102(b) to be proper, the reference(s) must recite each and every element of the invention as claimed. Applicants assert that Medenica does not teach the methods of the present invention as currently claimed and that there are distinct differences between the teachings of Medenica and the present application.

For example, applicants assert that Medenica teaches the extract of *Nigella sativa* **for inhibiting cancer cell growth.** Applicants further assert that Medenica **neither teaches nor suggests the use of a pharmaceutical composition** comprising a therapeutically effective amount of at least one of the botanical plants selected from the group consisting of Actaea rubra, Anemone hepatica, Anemone nemorosa, Nigella sativa, and Ranunculus arvensis, or extracts thereof, and a pharmaceutically acceptable carrier **for treating patients having advanced stage hepatitis characterized by fibrosis and cirrhosis and for increasing the number of immune cells and platelets in patients having advanced stage hepatitis characterized by fibrosis and cirrhosis, wherein the patients are in stage 4-6 of the disease process**.

In addition, Medenica teaches that the amount of extract from the seeds to be delivered to an individual should be in the range of about 20-40 grams, as shown in column 5, lines 53-57 and in column 35, lines 40-43. Given an average weight of 70 kg,

the dosage needed for treatment would range from about 0.3g/kg to about 0.6g/kg. This is far beyond the range envisioned for the extracts of the present invention. As shown on page 31, paragraph [0094], the dosage envisioned for the present invention is about 20-500 ug/kg administered intravenously.

Applicants submit that based on the foregoing amendment to the claims, Medenica **does not teach or suggest** the compositions of the instant invention.

Withdrawal of the rejection under 35 U.S.C. 102(b) is respectfully requested.

B. Claims 1, 2, 5 and 7 are rejected under 35 U.S.C. 102(b) as being unpatentable over Shawkat (U.S. 5,648,089). The Examiner alleges that Shawkat teaches using *Nigella sativa* in an oral herb composition to treat patients diagnosed with active Hepatitis B and Hepatitis C.

Shawkat

Applicants assert that Shawkat teaches an herbal combination for treating viral hepatitis. This combination contains a mixture of extracts from nine different plants, one of which is *Nigella sativa.* The extract of *Nigella sativa* is obtained from the seeds of the plant. Furthermore, the concentration of the extract from *Nigella sativa* is 10%.

Claim Amendments and Arguments in Support of Patentability over Shawkat et al.

Applicants respectfully traverse the Examiner's rejection and again assert that in order for a rejection under 35 U.S.C. 102(b) to be proper, the reference(s) must recite each and every element of the invention as claimed. Applicants assert that Shawkat does not teach the methods of the present invention as currently claimed and that there are distinct differences between the teachings of Shawkat and the present application.

For example, applicants assert that Shawkat teaches an herbal combination containing a mixture of extracts from nine different plants, one of which is *Nigella sativa.* Furthermore, the Examiner's attention is drawn to U.S. 5,648,089 to column 1, lines 60-61, whereby Shawkat teaches that the extract of *Nigella sativa* is obtained from the seeds of the plant, and is present in the mixture at a concentration of 10%. The mixture of botanicals is useful for treating viral hepatitis.

Applicants assert that Shawkat **neither teaches nor suggests the use of a pharmaceutical composition comprising a therapeutically effective amount of at**

least one of the botanical plants selected from the group consisting of Actaea rubra, Anemone hepatica, Anemone nemorosa, Nigella sativa, and Ranunculus arvensis, or extracts thereof, and a pharmaceutically acceptable carrier for treating patients having advanced stage hepatitis characterized by fibrosis and cirrhosis and for increasing the number of immune cells and platelets in patients having advanced stage hepatitis characterized by fibrosis and cirrhosis, wherein the patients are in stage 4-6 of the disease process.

Applicants have also submitted herewith a declaration under 37 CFR 1.132 signed by Dr. Ismail Elchagea, attesting to the fact that no one to date has ever demonstrated that the extracts of the plants presently claimed have ever shown an improvement in liver function or immunological function at such a late stage of the disease process, particularly when there is evidence of fibrosis and cirrhosis. Applicants submit that based on the foregoing amendment to the claims, Shawkat does not teach or suggest the methods of the instant invention, as currently claimed.

Withdrawal of the rejection under 35 U.S.C. 102(b) is respectfully requested.

Rejection Under 35 U.S.C. §103 (a)

A. Claims 1, 3-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Medenica (U.S. 5,653,981). The Examiner alleges that Medenica teaches using an extract of *Nigella sativa* for increasing immune system function. The Examiner further alleges that Medenica teaches that the extract of *Nigella sativa* may be administered intramuscularly, subcutaneously, intravenously, by tablet, by capsule, or suppositories.

The Examiner fails to set forth a proper prima facie case of obviousness

Applicants remind the Examiner that a rejection under 35 U.S.C. §103 is proper only when a prior art reference alone or in combination with a second prior art reference renders the invention obvious. Applicants further remind the Examiner that a rejection based upon a combination of references is not proper unless the following three criteria are met: 1) the references in combination teach every single element of the invention as claimed; 2) there must be some suggestion or motivation in the prior art to combine the

references to reach the invention as claimed; and 3) there must be a reasonable expectation of success in making the combination to reach the invention as claimed.

The Examiner never explicitly states a rejection of any claims that is based on Medenica in view of Shawkat. The Examiner admits that Medenica does not teach or suggest the ingredients in the dosage forms or the amounts claimed by Applicant. The Examiner alleges that the dosage form or amount of a specific ingredient in a composition is the result effective parameter that a person of ordinary skill in the art would routinely optimize. The Examiner alleges that optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. Applicants respectfully submit that it is no more than obvious to try different dosage forms or ingredients, and obvious to try has never been the proper standard for assessing obviousness. Even if, *assuming arguendo*, one of ordinary skill in the art found such dosage forms or ingredients obvious to use, the present invention is still patentable for at least the following two reasons:

1. There simply is no teaching or suggestion of a pharmaceutical composition comprising a therapeutically effective amount of at least one of the botanical plants selected from the group consisting of Actaea rubra, Anemone hepatica, Anemone nemorosa, Nigella sativa, and Ranunculus arvensis, or extracts thereof, and a pharmaceutically acceptable carrier **for treating patients having advanced stage hepatitis characterized by fibrosis and cirrhosis and for increasing the number of immune cells and platelets in patients having advanced stage hepatitis characterized by fibrosis and cirrhosis, wherein the patients are in stage 4-6 of the disease process**.

2. There is no teaching or suggestion that one must use a concentration of at **least 20% w/v** to achieve the desired clinical effects for treating advanced stage hepatitis patients having reached stage 4-6 of the disease process or for increasing the number of immune cells or platelets in this patient population.

Based on the foregoing, withdrawal of the rejection under 35 U.S.C. 103(a) is respectfully requested.

B. Claims 1, 3-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shawkat (U.S. 5,648,089). The Examiner alleges that Shawkat teaches using *Nigella sativa* in an oral herb composition to treat patients diagnosed with active Hepatitis B and Hepatitis C.

The Examiner fails to set forth a proper prima facie case of obviousness

As noted above, Applicants remind the Examiner that a rejection under 35 U.S.C. §103 is proper only when a prior art reference alone or in combination with a second prior art reference renders the invention obvious. Applicants further remind the Examiner that a rejection based upon a combination of references is not proper unless the following three criteria are met: 1) the references in combination teach every single element of the invention as claimed; 2) there must be some suggestion or motivation in the prior art to combine the references to reach the invention as claimed; and 3) there must be a reasonable expectation of success in making the combination to reach the invention as claimed.

As noted above, the Examiner never explicitly states a rejection of any claims that is based on Shawkat in view of Medenica. The Examiner admits that Shawkat does not teach or suggest the ingredients in the dosage forms or the amounts claimed by Applicant. The Examiner alleges that the dosage form or amount of a specific ingredient in a composition is the result effective parameter that a person of ordinary skill in the art would routinely optimize. The Examiner alleges that optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. Applicants respectfully submit that it is no more than obvious to try different dosage forms or ingredients, and obvious to try has never been the proper standard for assessing obviousness. Even if, *assuming arguendo*, one of ordinary skill in the art found such dosage forms or ingredients obvious to use, the present invention is still patentable for at least the following two reasons:

1. There simply is no teaching or suggestion of a pharmaceutical composition comprising a therapeutically effective amount of at least one of the botanical plants selected from the group consisting of Actaea rubra, Anemone hepatica, Anemone nemorosa, Nigella sativa, and Ranunculus arvensis, or extracts thereof, and a pharmaceutically acceptable carrier **for treating patients having advanced stage**

hepatitis characterized by fibrosis and cirrhosis and for increasing the number of immune cells and platelets in patients having advanced stage hepatitis characterized by fibrosis and cirrhosis, wherein the patients are in stage 4-6 of the disease process.

2. There is no teaching or suggestion that one must use a concentration of at **least 20% w/v** to achieve the desired clinical effects for treating advanced stage hepatitis patients having reached stage 4-6 of the disease process or for increasing the number of immune cells or platelets in this patient population.

Neither Shawkat nor Medenica teach a pharmaceutical composition for treating stage 4-6 (advanced stage) hepatitis patients having evidence of liver fibrosis and/or cirrhosis. Nor do they teach a pharmaceutical composition for increasing the number of immune cells and platelets in this patient population. Further, neither Shawkat nor Medenica teach or suggest an effective concentration of at least 20% w/v. Therefore, there would have been no motivation to combine the teachings of Shawkat and Medenica in order to practice the compositions of the present invention.

Withdrawal of the rejection under 35 U.S.C. 103(a) is respectfully requested.

Furthermore, applicants provide herewith a declaration under 37 C.F.R. 1.132, signed by Dr. Ismail Elchagea, attesting to the advantages of a pharmaceutical composition such as that presently claimed for treating patients having such advanced stage hepatitis. No one to date has demonstrated that the compositions as claimed could have such a dramatic effect on both the histopathological effects, as well as on the immune function in hepatitis patients at such a late stage of the hepatitis disease process, particularly when fibrosis and cirrhosis are evident. Furthermore, the dose used for treating these late stage hepatitis patients differs significantly from the doses of Shawkat and Medenica. Accordingly, the dosages taught by Medenica and Shawkat in all likelihood would not prove effective if used following extraction of the active moiety from the whole plant, since in both cases, lower concentrations, in particular, 2.2% and 10%, were used, respectively. The higher doses of the composition as used by Applicants of the present invention were necessitated by the advanced stage of the disease for which treatment was desired. More particularly, due to the presence of active fibrosis and cirrhosis in these advanced stage hepatitis patients, the lower doses taught by Shawkat and Medenica in all likelihood, would not have been effective. In addition,

neither Shawkat nor Medenica have demonstrated effects of the plant composition as presently claimed, on platelet counts in this patient population.

Applicants assert that the teachings of Shawkat and Medenica, when used alone or in combination, do not teach or suggest the compositions of the presently claimed invention. Applicants further assert that the teachings of Shawkat and Medenica, when used alone or in combination, would not motivate one of skill in the art to practice the instant invention, as presently claimed.

Based on the foregoing, withdrawal of the rejection is respectfully requested.

Fees

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or to credit any overpayments.

Conclusion

Applicants believe that in view of the foregoing, the claims are in condition for allowance. Withdrawal of the rejections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

Veronica Mallon, Ph.D.
Agent for Applicants
Registration No. 52,491

KLAUBER & JACKSON
411 Hackensack Avenue
Hackensack, NJ 07601
(201) 487-5800
Attachments: Declaration under 37 CFR 1.132 with Exhibit A (10 figures)